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EDITORIAL COMMENT

Anger, Depression, and Anxiety in Cardiac Patients

The Complexity of Individual Differences in Psychological Risk*

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A couple of years ago, a large meta-analytic review concluded that depression can be considered a prognostic factor in coronary heart disease (CHD) (1). Depression has also been associated with increased mortality in heart failure (2). However, although a recent advisory from a number of councils of the American Heart Association recommends routine screening for depression of CHD patients in clinical practice (3), a systematic review published 1 month later did not find evidence for or against this recommendation (4). In this issue of the *Journal*, Chida and Steptoe (5) report on a meta-analysis of prospective studies on the association between another psychological factor, anger/hostility, and the risk of CHD.

See page 936

Anger, hostility, and CHD. In their meta-analysis of 25 prospective studies on the incidence of CHD and 20 studies of patients with established CHD, the authors found that anger/hostility was associated with a 20% increased risk of both incident CHD in initially healthy individuals and poor prognosis in CHD patients (5). On the basis of these findings, they conclude that anger/hostility is associated with CHD outcomes and that intervention should focus on the psychological management of anger/hostility in the prevention and treatment of CHD.

The authors are to be commended for having conducted this methodologically well-performed meta-analysis supporting the role of psychological factors in the onset and prognosis of CHD. Their study provides an important contribution to the cardiovascular literature, because traits such as anger/hostility are less likely to arise as a consequence of somatic disease. Although depression might be confounded by left ventricular dysfunction in patients with CHD (1), anger/hostility measures do not include somatic symptoms. Although the risk incurred by anger/hostility of 20% is relatively small, when placed in the context of the 11% risk associated with von Willebrand factor as a predictor of incident CHD in the Reykjavik study (6), this effect attributed to a psychological factor seems notable.

It could be argued, however, that anger and hostility do not comprise 1 behavioral construct, as was also posited by the authors. Hence, merging of the 2 factors into 1 construct obscures any differential cardiotoxic effects that both psychological factors might have. This might also have implications for interventions, as seen in the current debate on depression as a potential cardiovascular risk factor (7). Researchers focusing on the role of depression are increasingly recognizing that depression in cardiac patients does not involve a homogeneous diagnostic category but might comprise distinctly different subtypes and is qualitatively different from depression seen in psychiatric patients. Some manifestations of depression might even reflect the severity of cardiac disease (1). In other words, pinpointing the most cardiotoxic depressive symptoms and whether it is incident, recurrent, or chronic depression that incurs an increased risk might change how we design intervention trials targeting depression in CHD (7).

The complex network of psychological factors. Chida and Steptoe (5) focused on 1 psychological factor, but in real life, psychological factors might cluster together within individuals to substantially increase the risk of clinical events (8). Arguably, it is difficult to conduct a meta-analysis that catches this complexity. However, different psychological factors might promote CHD (9–13). Although anxiety is common among cardiovascular patients and increases the risk of cardiac events if untreated (9–11), only 1 of 3 anxious patients is asked about such symptoms. Recently, Ladwig et al. (12) showed that treatment with an implantable cardioverter defibrillator might induce post-traumatic stress and that this stress independently predicts a greater risk for mortality. In a state-of-the-art paper previously published in the *Journal*, Dimsdale (13) discusses how psychological stress might lead to pathophysiological changes that ultimately become manifest as hard medical events, such as mortality and morbidity. Hence, it is important to take a moment to acknowledge the existence of this complexity and what the consequences might be if we do not.

Clinical research on the modulation of inflammation in heart failure might serve as an illustrative analogy. Despite evidence that increased levels of the pro-inflammatory cytokine tumor necrosis factor-α and its receptors predict poor prognosis in heart failure, clinical trials targeting this specific cytokine produced disappointing findings. However, as shown in the ACCLAIM (Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy) trial, focusing on cytokine networks rather than specific or single cytokines might be a more successful approach,

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because this broad immunomodulation therapy led to improved survival (14).

Appreciating individual differences in risk. As an analogy, the role of psychological factors in the onset and progression of CHD should also be studied in concert rather than using an individual risk factor approach (8). The ensuing question is then: how can physicians deal with the complexity of improving patient outcomes by placing all of these psychological factors in the forefront of clinical cardiology practice?

One of the answers might be to acknowledge that the psychological risk is not uniform across all patients and that psychological factors might cluster together within individuals (8). As Dimsdale notes, "vulnerability and resilience factors play a role in amplifying or dampening" the effects of psychological factors on the heart (13), with these factors belonging to the realm of personality (11,15). A broad, stable disposition to experience psychological distress has been associated with poor outcome after percutaneous coronary intervention in the RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) registry (15). This broad disposition toward psychological distress might also partly explain individual differences in physiological stress-reactivity, such as an increased level of the stress-hormone cortisol in patients with CHD (16). Currently, these individual differences are largely ignored in clinical research and practice, but they could be assessed with brief and standardized self-report measures and would do away with a single risk factor approach.

Broadening the focus of intervention. Needless to say, the challenges we face are numerous. A major challenge is to develop more effective treatments for cardiac patients at risk of poor prognosis and quality of life due to their psychological profile. Interventions might need to be more broadly focused, targeting the various emotional and social difficulties that patients face (17), hopefully with beneficial results similar to those of the ACCLAIM trial (14). It might be important to tailor interventions to the individual patient to find out what works for whom. Comprehensive cardiac rehabilitation offers several opportunities in this context, but some patients with psychological comorbidity might need more intensive treatment and should be referred to specialized healthcare professionals.

In future trials, it is important to pay particular attention to nonresponders to intervention, because these patients have been shown to be at a higher risk of late mortality compared with responders (18). Although as yet we might not have the answer as to how to moderate the psychological risk of patients in terms of improved survival, let us not forget that psychological factors also serve as barriers for lifestyle changes (such as smoking cessation), treatment adherence, and participation in outpatient rehabilitation programs, and have an adverse influence on health status. Hence, survival should be the only end point neither for research purposes nor in clinical practice when seeking to moderate the impact of the psychological factor.

To conclude, the meta-analysis by Chida and Steptoe (5) carries with it several important messages, including that: 1) psychological factors *do* matter in CHD; 2) pursuing vulnerability and resilience factors might be particularly worthwhile, because they might be less prone to confounding by disease severity; and 3) although we might be far from having all of the answers, the risk associated with psychological factors is similar to that of other clinical risk indicators.

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